Description of Visfatin Adipokine and its Roles on Inflammation and Coronary Heart Disease: A Review Study

Assist. Prof.Dr. Wijdan Rajh Hamza Al-Kraity^{1*}; Ali Hussein Faisal²; Ali Nabeel Khaleel³; Mahmoud Tuama Naeaam⁴; Ali Sattar Jabar⁵

^{1,2,3,4,5}Department Medical Laboratories Techniques, Al-Toosi University College, Iraq

*e-mail: dr.wijdan_rajh@altoosi.edu.iq

ABSTRACT

Coronary heart disease (CHD) is a generic designation for a group of related syndromes resulting from myocardial ischemia – an imbalance between cardiac blood supply (perfusion) and myocardial oxygen demand. Visfatin (VF) is a recently discovered adipokine with different functions, Visfatin is mainly found in visceral adipose tissue and mimics insulin in lowering plasma glucose levels and, Visfatin emerges as a player in the development and progression of atherosclerotic lesions by directly promoting smooth muscle cell proliferation, Aberrant angiogenesis is now considered a feature of the atherogenic process in both coronary and carotid diseases. This adipokine was previously known as a pre-B-cell colony-enhancing factor (PBEF) or Nicotinamide phosphoribosyltransferase (NAMPTase or Nampt) an enzyme that in humans is encoded by the NAMPT gene and demonstrated to be an intracellular protein with a key enzyme role in nicotinamide adenine dinucleotide (NAD)

Keywords: Coronary heart diseases, Visfatin, adipokine, pre-B-cell colony-enhancing factor (PBEF)

Article Information

Received: January 2, 2021; Revised: : February 26, 2021; Online: : March 1, 2021

INTRODUCTION

Coronary heart diseases (CHD) are the most common cause of morbidity and mortality in most countries (Sebregts *et al.*, 2000), also due to the significant impact of coronary heart disease, it is important for identifying the determinants of risk for developing this disease, coronary artery diseases are the generic designation for the three forms of cardiac diseases, i.e., angina pectoris {unstable angina (UA), stable angina (SA)}, sudden cardiac death and acute myocardial infarction (AMI), In most cases, the abnormal outcomes from inadequate blood flow resultant lead to the development of atherosclerosis causing in narrowing of the coronary arteries, thus, CHD is {also often called coronary artery disease (CAD) or ischemic heart disease (IHD)} (Ryden *et al.*, 2007; Naveen, 2009).

Adipokines and proinflammatory molecules that affect cardiovascular functions through not only as endocrine manner, but also by autocrine and paracrine mechanisms (De-Clercq *et al.*, 2008). Consequence ends up with cytokine-mediated and systemic inflammation and atherosclerosis, Various studies revealed association of visfatin with

inflammation (Moschen *et al.*, 2007), metabolic syndrome (Shaker *et al.*, 2011), endothelial dysfunction (Dahl *et al.*, 2007), atherosclerosis (Filippatos *et al.*, 2010) and ischemia reperfusion injury (Mazaherioun *et al.*, 2012; Filippatos *et al.*, 2013).

Visfatin (VF) is a recently discovered adipokine with different functions, Visfatin is mainly found in visceral adipose tissue and mimics insulin in lowering plasma glucose levels (Fukuhara *et al.*, 2005; Shaker *et al.*, 2011). Visfatin, other than the fat tissue, is expressed by various other cells and tissues such as neutrophils, liver, heart and muscles as well as accepted as a growth factor for the maturation of pro-cells of the B-lymphocytes (Kitani *et al.*, 2003; Gürsoy *et al.*, 2014).

This adipokine was previously known as pre-B-cell colony-enhancing factor (PBEF) or Nicotinamide phosphoribosyltransferase (NAMPTase or Nampt) an enzyme that in humans is encoded by the NAMPT gene and demonstrated to be an intracellular protein with a key enzyme role

in nicotinamide adenine dinucleotide (NAD) synthesis (Samal *et al.*, 1994; Fukuhara *et al.*, 2005).

Visfatin

Definition and functions

Visfatin is one of the newly discovered adipokines, which is 52 kilodalton (kDa) protein, Visfatin was first described as pre-B cell colony enhancing factor (PBEF) and Nicotinamide phosphoribosyl transferase (NAMPT) because it is involved in nicotinamide adenine dinucleotide synthesis from nicotinamide (Matsuda *et al.*, 2005), it has insulin-mimetic properties (Stofkova *et al.*, 2010). Recently, PBEF was identified by Fukuhara *et al.* (2005), as visfatin a novel adipokine - a protein mediator secreted by fat cells (high levels of expression in visceral fat cells). However, the visceral fat is not the only tissue where Visfatin is expressed. Leucocytes of peripheral blood (Samal *et al.*, 1994) or adipose tissue macrophages (Curat *et al.*, 2006), hepatocytes (Garten *et al.*, 2010) or skeletal muscles (Costford *et al.*, 2010) also participate in Visfatin production and may influence Visfatin plasma levels.

The product of Visfatin/PBEF gene was initially identified by Samal and his colleagues in (1994) as a cytokine subsequently named pre-B-cell colony-enhancing factor (PBEF) that is expressed in lymphocytes of peripheral blood and plays a role in lymphocytes maturation and inhibition of neutrophil apoptosis (Jia *et al.*, 2004)

Visfatin role in immunity was explained as its gene was expressed in lymphocyte cells and it also induced the production of interleukins such as IL-1B, IL-6 and Tumor necrosis factor which are pro-inflammatory cytokines and IL-1 α and IL-10 which are anti-inflammatory cytokines (Moschen *et al.*, 2010; Olszanecka *et al.*, 2011) and it had an important roles in metabolism, aging and inflammation (Wang *et al.*, 2011).

CHD diseases lead to the release of inflammatory mediators from the damaged tissue into saliva and other biological fluid (Trivedi *et al.*, 2012). There is a direct association between visfatin levels and increased cardiovascular disease (Filippatos *et al.*, 2013) and it had a role in many pathophysiological processes that eventually lead to cardiovascular disease such as hypertension and atherosclerosis (Omer and Mahmood, 2016).

Structure

Visfatin is a 52-kD a protein (Flier *et al.*, 2007), is active as a dimer, with each monomer containing 491 amino acids in humans, This has been proved by the fact that visfatin/PBEF/Nampt has two active sites at the interface of the dimeric protein, suggesting that dimerization is essential for the

catalytic activity of the enzyme (Wang *et al.*, 2006). Each monomer contains 19 β -strands and 13 α -helices and is organized into two structural domains (KIM *et al.*, 2006). Show figure (1).

Figure (1): The crystal structure of visfatin adapted by (Raman, 2013).

The fragment-based identification of two novel and potent biochemical inhibitors of the nicotinamide phosphoribosyltransferase (NAMPT) enzyme is described in study of (Dragovich *et al.*, 2014). These compounds (51 and 63) incorporate an amide moiety derived from 3-aminopyridine, and are thus structurally distinct from other known anti-NAMPT agents. Each exhibits potent inhibition of NAMPT biochemical activity (IC_{50} = 19 and 15 nM, respectively) as well as robust antiproliferative properties in A2780 cell culture experiments (IC_{50} = 121 and 99 nM, respectively). Show the figure (2).

Figure (2): The chemical structure of visfatin, adapted by (Dragovich *et al.*, 2014)

Action on cardiovascular systems

1-Cell proliferation and angiogenesis

Proliferation of vascular smooth muscle cell (VSMC) is a hallmark of the development of atherosclerotic lesions. Importantly, perivascular visfatin/Nampt can act as a growth factor in vascular smooth muscle cells, promoting cell proliferation in aortic smooth muscle cells though Nampt enzymatic activity (Wang *et al.*, 2009).

Visfatin/Nampt emerges as a player in the development and progression of atherosclerotic lesions by directly promoting smooth muscle cell proliferation. Aberrant angiogenesis is now considered a feature of the atherogenic process in both coronary and carotid diseases (Moulton, 2006). In this line, it has also been described that VEGF synthesis and secretion as well as the expression of the VEGF receptor 2, which has been proposed to mediate the angiogenic actions of VEGF (Adya *et al.*, 2008).

Besides VEGF, visfatin/Nampt upregulates the production of other proangiogenic soluble factors, such as fibroblast growth factor-2 (FGF-2), MCP-1, and IL-6, in endothelial cells (Lee *et al.*, 2009). Indeed, both MCP-1 and FGF-2 have also been identified as mediators of visfatin/Nampt-induced angiogenesis (Bae *et al.*, 2009). Show figure (3).

2. Inflammation, atherogenesis and coronary heart disease.

Growing scientific evidence supports that visfatin/Nampt can directly promote vascular inflammation by activating different cell types including endothelial cells and vascular smooth muscle cells. Moreover, visfatin/Nampt can also contribute to vascular inflammation through its immunomodulatory properties on immune cells (Moschen *et al.*, 2007). Thus, visfatin/Nampt can exert direct actions on monocytes. Hence, visfatin/Nampt promotes the synthesis and release of proinflammatory cytokines, such as tumor necrosis factor- α (TNF- α) and IL-8, by peripheral mononuclear cells (Dahl *et al.*, 2007).

Additionally, visfatin/Nampt promotes macrophage survival (Li *et al.*, 2008) which may help perpetuating vascular inflammation. In cultured

human vascular smooth muscle cells, our group demonstrated for the first time that visfatin/Nampt could directly exert inflammatory effects. Thus, exogenous administration of visfatin/Nampt activates ERK 1/2 and NF- κ B, resulting in enhanced expression of the inducible nitric oxide synthase (iNOS) (Romacho *et al.*, 2009). The iNOS is a pro-inflammatory enzyme contributing to dysregulated NO production and subsequent peroxynitrite formation. Thus, iNOS induction plays a key role in endothelial dysfunction and vascular injury in diabetes-related vascular complications (Pacher *et al.*, 2005). Show figure (3).

Figure (3): Diagram summarizing the main reported direct actions of visfatin/Nampt in cells in the cardiovascular system, adapted by (Romacho *et al.*, 2013)

CONCLUSION

The visfatin is consider as a inflammatory markers that related with obesity and atherosclerosis, endothelial dysfunction and coronary heart disease.

ACKNOWLEDGMENT

Not applicable.

REFERENCES

- Adya, R.;** Tan, B.; Pun, A.; Chen, J. and Rande, H. (2008). Visfatin induces human endothelial VEGF and MMP-2/9 production via MAPK and PI3K/Akt signalling pathways: novel insights into visfatin-induced angiogenesis. *Cardiovascular Research*, 78 (2):356–365, 2008.
- Bae, Y.;** Bae, M.; Kim, S.; Lee, J.; Wee, H. and Bae, S. (2009). Upregulation of fibroblast growth factor-2 by visfatin that promotes endothelial angiogenesis. *Biochemical and Biophysical Research Communications*, 379.(2): 206–211.
- Costford, S.R.;** Bajpey, S.; Pasarica, M.; Albarado, D.C.; Thomas, S.C.; Xie, H. and *et al.* (2010). Skeletal muscle NAMPT is induced by exercise in humans. *American Journal of Physiology –Endocrinology and Metabolism*, 298(1): 117–26.
- Curat , C.A.;** Wegner, V.; Sengen, C.; Miranville, A.; Tonus, C.; Busse, R. and *et al.* (2006). Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. *Diabetologia*, 49(4): 744-747.
- Dahl, T.;** Yndestad, A.; Skjelland, M. and *et al.* (2007). Increased expression of visfatin in macrophages of human unstable carotid and coronary atherosclerosis: possible role in inflammation and plaque destabilization. *Circulation*, 115(8) : 972–980.
- De-Clercq, V.;** Taylor, C. and Zahradka, P. (2008). Adipose tissue: the link between obesity and cardiovascular disease. *Cardiovasc. Hematol. Disord. Drug Targets*, 8:228-37.
- Dragovich, P.;** Zhao, G.; Baumeister T.; Bravo, B. and Giannetti, A. (2014). Fragment-based design of 3-aminopyridine-derived amides as potent inhibitors of human nicotinamide phosphoribosyltransferase (NAMPT). *Bioorganic & Medicinal Chemistry Letters*, 24, (3): 954-962.
- Filippatos, T.D.;** Rande, H.S.; Derdemezis, C.S.; Elisaf, M.S. and Mikhailidis, D.P. (2010). Visfatin/PBEF and atherosclerosis-related diseases. *Curr. Vasc. Pharmacol.*, 8:12-28.
- **Filippatos, T.D.;** Tsimihodimos, V.; Derdemezis, C.S.; **Gazi, I.F.;** Saougos, V.; Mikhailidis, D.P. and *et al.* (2013). Increased plasma visfatin concentration is a marker of an atherogenic metabolic profile. *Nutr. Metab. Cardiovasc. Dis.*, 23:330-6.
- Flier, J.s.;** Flier, E.m.; Wiener, C.; Fauci A.S. and *et al.* (2007). Biology of Obesity. In: Harrison's Principles of Internal Medicine . *The McGraw-Hill companies Inc, New York*, pp. 462- 472.
- Fukuhara, A.;** Matsuda, M.; Nishizawa, M.; Segawa, K.; Tanaka, M. and *et al.* (2005). Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. *Science*, 307: 426-430.
- Garten, A.;** Petzold, S.; Barnikol-Oettler, A.; Korner, A.; Thasler, W.E.; Kratzsch, J. and *et al.* (2010). Nicotinamide phosphoribosyltransferase (NAMPT/PBEF/visfatin) is constitutively released from human hepatocytes. *Biochemical and Biophysical Research Communications*, 2010;391(January (1)):376–81.
- Gürsoy, M.;** Duygu, E.; Hökenek, A.F.; Gülcan, F. and Kınoglu, B. (2014). Serum Visfatin Levels and Coronary Artery Disease. *Koşuyolu Heart Journal*, 17(2):95-99.
- Jia, S.H.;** Li, Y.; Parodo, J.; Kapus, A.; Fan, L.; Rotstein, O.D. and *et al.* (2004). Pre-B cell colony enhancing factor inhibits neutrophil apoptosis in experimental inflammation and clinical sepsis. *Journal of Clinical Investigation*, 113(9):1318–27.
- Kim, M.k.;** Lee, J.h.; Kim, H.; Park, S.j.; Kim, S.h.; Kang, G.b. and *et al.* (2006). Crystal structure of visfatin/pre-B cell colony-enhancing factor 1/nicotinamide phosphoribosyltransferase, free and in complex with the anti-cancer agent FK-866. *Mol. Biol.*, 362: 66-77.
- Kitani, T.;** Okuno, S. and Fujisawa, H. (2003). Growth phasedependent changes in the subcellular localization of pre-B-cell colony-enhancing factor. *FEBS. Lett.*, 544:74-8.
- Lee, W.;** Wu, C.; Lin, H. and *et al.* (2009). Visfatin-induced expression of inflammatory mediators in human endothelial cells through the NF-kappaB pathway. *International Journal of Obesity*, 33 (4):465–472.
- Li, Y.;** Zhang, Y.; Dorweiler, B. and *et al.* (2008). Extracellular nampt promotes macrophage survival via a nonenzymatic interleukin- 6/STAT3 signaling mechanism. *Journal of Biological Chemistry*, 283(50):34833–34843.
- Matsuda, F. and Nishizawa, M. et al.** (2005). Visfatin: a protein secreted by visceral fat that Mimics the effects of insulin. *Sci.*, 2005; 307:426–30.
- Mazaherioun, M.;** Hosseinzadeh-Attar, M.J.; Janani, L.; Vasheghani Farahani, A.; Rezvan, N.; Karbaschian, Z. and *et al.* (2012). Elevated serum visfatin levels in patients with acute myocardial infarction. *Arch. Iran Med.*, 15(11): 688 – 692.
- Moschen, A. .;** Kaser, A.; Enrich, B. and *et al.* (2007). “Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. *Journal of Immunology*, 178(3): 1748– 1758.
- Moschen., AR.;** Gerner, R.R. and Tilg, H. (2010). Pre-B cell colony enhancing factor in inflammation and obesity –related disorders. *Curr. Pharm. Des.*, 16(17):1913-20.

- Moulton, K.S.**(2006). Angiogenesis in atherosclerosis: gathering evidence beyond speculation. *Current Opinion in Lipidology*, 17(5):548–555.
- Naveen, G.** (2009). A study of lipid profile in smokers and it is association in ischemic heart disease, *Dissertation, M.D. (General Medicine)*, P39.
- Olszanecka, G.;** Linianowicz, M.; Kocelak, P.; Janowska, J.; Skorupa, A.; Nylec, M. and Zahorska, M. (2011). Plasma visfatin and tumor necrosis factor –alpha level in metabolic syndrome. *Kardiol. Pol.*, 69(8):802-7.
- Omer, R. and Mahmood, M.** (2016). Correlation between Visfatin and Creatine Kinase Levels with Periodontal Health Status of Patients with Coronary Atherosclerosis and Chronic Periodontitis. (*J. Bagh. Coll. Dentistry*, 28(3):121-125)
- Raman, T.** (2013). Adipokines, structure of visfatin. *Health & Medicine, Technology J.*
- Romacho, T.;** Azcutia, V.; Vazquez-Bella, M.; Matesanz, N.; Cercas, E. and *et al.* (2009). Extracellular PBEF/NAMPT/visfatin activates pro-inflammatory signalling in human vascular smooth muscle cells through nicotinamide phosphoribosyltransferase activity. *Diabetologia*. 52 (11)2455–2463.
- Romacho, T.;** Sánchez-Ferrer, C. and Peiró, C. (2013). Visfatin/Nampt: An Adipokine with Cardiovascular Impact. *Mediators of Inflammation*, 15 pages.
- Rydén, L.;** Standl, E.; Bartnik, M.; Van den Berghe, G.; Betteridge J.; de Boer, M.J.; Cosentino, F. and Jönsson, B. (2007). Guidelines on diabetes, pre-diabetes, and cardiovascular diseases. *Eur. Heart J.*, 28, 88-136.
- Samal, B.;** Sun, Y.; Stearns, G.; Xie, C.; Suggs, S. and McNiece, I. (1994). Cloning and characterization of the cDNA encoding a novel human pre-B-cell colony-enhancing factor. *Molecular and Cellular Biology*, 14 (2):1431–7.
- Sebregts, E.H.;** Falger, P.R and Bar, F.W. (2000). Risk factor modification through non-pharmacological interventions in patients with coronary heart diseases. *Journal of Psychosomatic Research*, 48: 425- 41.
- Shaker, O.;** El-Shehaby, A.; Zakaria, A.; Mostafa, N.; Talaat, S.; Katsiki, N. and *et al.*(2011). Plasma visfatin and retinol binding protein-4 levels in patients with type 2 diabetes mellitus and their relationship to adiposity and fatty liver. *Clin. Biochem.*, 44:1457-63.
- Stofkova, A.** (2010). Resisiten and visfatin: regulators of insulin sensitivity, inflammation and immunity. *Endocr. Regul.*, 44: 25-36.
- Trivedi, D. and Chhaya, T.** (2012). Salivary proteome in periodontal diagnosis. *International. J. Pharma. and Bio.Sci.*, 2:5-9.
- Wang, L.S.;** Yan, J.J.; Tang, N.P.; Zhu, J.; Wang, Y.S. and *et al.*, (2011). polymorphism in the visfatin gene promoter is related to decreased plasma levels of inflammatory markers in patients with coronary artery disease. *Mol. Biol. Rep.*, 38(2): 819-25.
- Wang, P.;** Xu, T.; Guan, Y.; Su, D.; Fan, G. and C. Miao, C. (2009). Perivascular adipose tissue-derived visfatin is a vascular smooth muscle cell growth factor: role of nicotinamide mononucleotide, *Cardiovascular Research*, 81 (2): 370–380.
- Wang, T.;** Zhang, X.; Bheda, P.; Revollo, J.r.; Imai, S. and Wolberger, C. (2006). Structure of Nampt/PBEF/visfatin, a mammalian NAD⁺ biosynthetic enzyme. *Nat. Struct. Mol. Biol.* 13: 661-662.